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In Silico Screening of Murrayakoenigii Alkaloids Against SLC7A11 in Ferroptosis-Associated Pulmonary Fibrosis

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Abstract

Background:
Pulmonary fibrosis is a progressive disorder characterized by excessive extracellular-matrix deposition and loss of normal lung architecture. Ferroptosis, an iron-dependent form of regulated cell death associated with lipid peroxidation, has been implicated in pulmonary fibrotic injury. SLC7A11, a component of the cystine/glutamate antiporter system, contributes to cellular redox homeostasis and is relevant to ferroptosis biology.

Objective:
To computationally screen selected Murrayakoenigii-derived alkaloids for predicted interactions with SLC7A11 and assess selected drug-likeness, pharmacokinetic and toxicity properties.

Methods:
Murrayakoenigii leaves were defatted with petroleum ether and extracted with methanol by Soxhlet extraction. Preliminary phytochemical tests and Fourier-transform infrared (FTIR) spectroscopy were performed on the extract. Eight reported M. koenigii alkaloids were selected for in silico screening.
The SLC7A11 structure (PDB ID: 7EPZ) was retrieved from the RCSB Protein Data Bank, and a potential binding pocket was selected using DoGSiteScorer. Ligand docking was performed using AutoDock Vina, and interactions were visualized using BIOVIA Discovery Studio Visualizer. SwissADME, MolSoft and ProTox 3.0 were used for computational property and toxicity predictions.

Results:
Among the screened compounds, Murrayazoline showed the most favourable reported docking score against SLC7A11 (−9.1 kcal/mol), compared with −6.3 kcal/mol for pirfenidone. Reported nearby residues included ILE64, LYS67, ARG148, ILE165 and LEU385. Murrayazoline was predicted to have high gastrointestinal absorption and no blood–brain barrier penetration, but it also showed high lipophilicity, low predicted aqueous solubility (0.45 mg/L) and a MolSoft drug-likeness score of −0.62. ProTox 3.0 predicted an LD_{50} of 750 mg/kg (toxicity class 4) and flagged several toxicity endpoints for further investigation.

Conclusion:
The results identify Murrayazoline as a computational candidate for further evaluation against SLC7A11. Docking and ADME/toxicity predictions are hypothesis-generating and do not demonstrate target inhibition, antifibrotic efficacy or safety. Docking validation and experimental studies are needed.

Keywords:
Murrayakoenigii; Murrayazoline; SLC7A11; ferroptosis; pulmonary fibrosis; molecular docking; ADME.

I. Introduction

Pulmonary fibrosis is a chronic, progressive lung disorder in which repeated epithelial injury and aberrant tissue repair lead to fibroblast activation, extracellular-matrix accumulation and impaired respiratory function.

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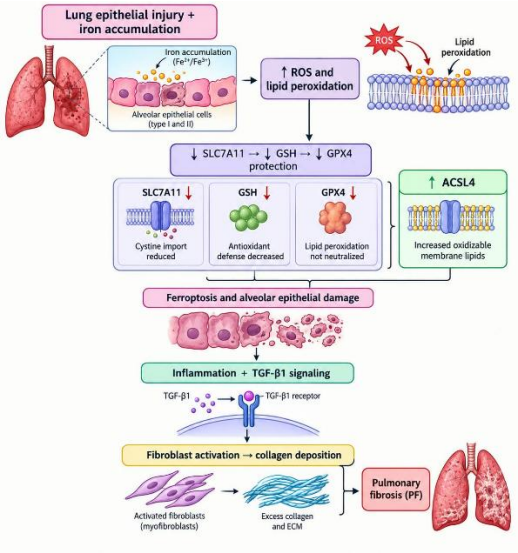


Idiopathic pulmonary fibrosis is associated with substantial morbidity and mortality, and currently available antifibrotic treatments can slow disease progression but do not reverse established fibrosis [1–3]. These limitations continue to motivate investigation of new molecular pathways and potential lead compounds.

Ferroptosis is a regulated, iron-dependent cell-death process associated with lipid peroxidation and failure of antioxidant defences [4,5]. The cystine/glutamate antiporter system, of which SLC7A11 (xCT) is a key component, supports cystine uptake and glutathione synthesis. Altered SLC7A11 activity can therefore influence cellular redox balance and susceptibility to ferroptosis. Emerging research has linked ferroptosis-related mechanisms, including changes in GPX4 activity, with pulmonary fibrotic injury [6,7]. The direction and consequences of SLC7A11 modulation may depend on the biological context, so predicted ligand binding alone cannot establish whether a compound would be beneficial in pulmonary fibrosis.

Murrayakoenigii (curry leaf) contains structurally diverse phytochemicals, including carbazole alkaloids. Reviews describe antioxidant, anti-inflammatory and other pharmacological activities for the plant and its constituents [8,9]. However, computational evaluation of selected M. koenigii alkaloids against ferroptosis-associated targets may help prioritize compounds for further investigation. Molecular docking can estimate plausible ligand poses and rank candidate interactions, but docking scores are model-dependent and should not be interpreted as experimentally measured binding affinities [10].

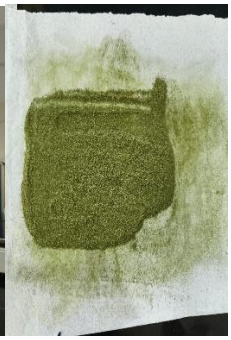
The present study combined preliminary analysis of a methanolic leaf extract with computational screening of selected M. koenigii alkaloids. The principal computational focus was SLC7A11 (PDB ID: 7EPZ), with pirfenidone used as a reference compound in the reported docking comparison. ADME, drug-likeness and toxicity predictions were also examined.

II. Materials and Methods

2.1 Plant collection, authentication and extraction

Fresh green leaves of Murrayakoenigii were collected from Bhaktipura village, Mayasandra, Attibele, Bengaluru, Karnataka, India. The plant material was authenticated by Dr. V. Rama Rao, Research Officer, Department of Botany, Central Ayurveda Research Institute, Government of India. The leaves were washed, dried and powdered. Fifty grams of powdered material was defatted with 500 mL petroleum ether in a Soxhlet apparatus for approximately 8 h at a reported heating temperature of 40 °C.

The defatted material was dried and extracted with 500 mL methanol in a Soxhlet apparatus for approximately 8 h. The methanol was evaporated at a reported hot-plate temperature of 20–30 °C, and the



residue was collected for further analysis. The extract yield and voucher specimen number were

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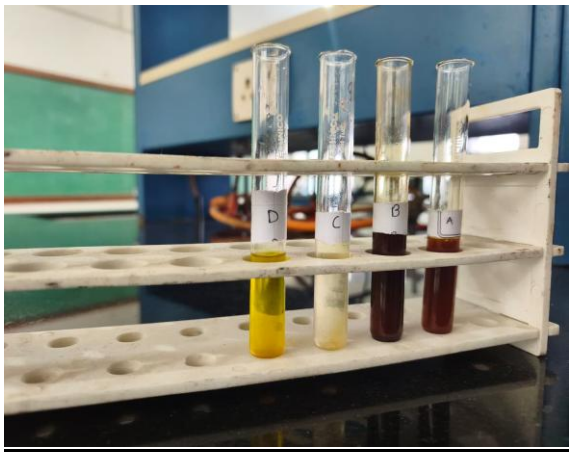
not reported in the thesis and should be added if available.

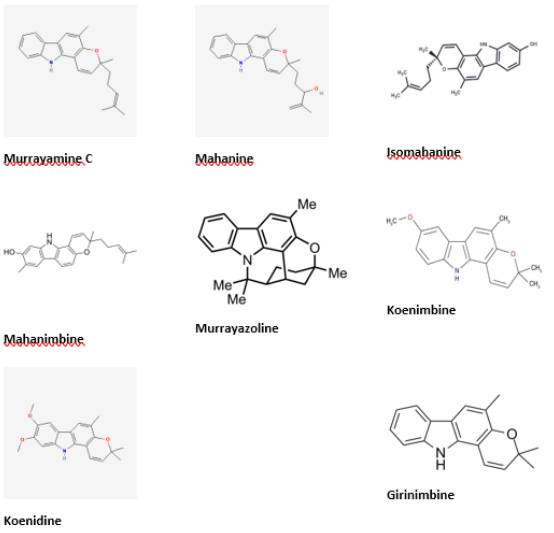
2.2 Preliminary phytochemical tests and FTIR

Preliminary chemical tests were performed on the plant extract according to the procedures recorded in the project thesis. FTIR spectroscopy was used to record absorption bands and infer possible functional groups. The thesis reports broad absorption regions at 3270–3300 cm^{-1}, around 2900 cm^{-1}, around 1600 cm^{-1}, 1400–1300 cm^{-1}, 1250–1000 cm^{-1} and 800–700 cm^{-1}. These bands were interpreted as potentially consistent with O–H, aliphatic C–H, aromatic or overlapping C=C, bending and C–O-related vibrations. FTIR of a crude extract does not identify individual compounds or confirm that Murrayazoline is present in the extract.



2.3 Selection of phytochemicals and target structure

Eight phytochemicals reported for M. koenigii were selected for computational evaluation: Murrayamine C, mahanine, isomahanine, Murrayazoline, mahanimbine, koenimbine, koenidine and girinimbine.



The ligand structures were retrieved from PubChem in SDF format. The human SLC7A11-containing structure was retrieved from the RCSB Protein Data Bank using PDB ID 7EPZ. Potential binding pockets were evaluated using DoGSiteScorer; pocket P0 was selected based on a reported drug score of 0.85, volume of 815.94 $Å^3$ and surface area of 981.45 $Å^2$.

2.4 Ligand preparation, docking and interaction analysis

Ligand structures were converted and energy-minimized using Open Babel. Protein preparation was described as removal of unwanted molecules, addition of hydrogen atoms and assignment of atomic charges. Molecular docking was performed with AutoDock Vina, and docking scores were reported in kcal/mol. The selected complexes were inspected using BIOVIA Discovery Studio Visualizer to identify nearby residues and predicted non-covalent contacts. Pirfenidone was used as a reference compound. The thesis does not provide a complete record of the software versions, docking exhaustiveness, grid-box coordinates and dimensions, retained poses, random seed, or a redocking/RMSD validation procedure; these details should be recovered from the original files or repeated analysis before journal submission.

2.5 ADME, drug-likeness and toxicity prediction

SwissADME and MolSoft were used to estimate physicochemical and drug-likeness properties. ProTox 3.0 was used to predict toxicity class, LD_{50} and selected toxicity endpoints. These outputs are

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computational predictions and were not experimentally validated in this study.

2.6 Data analysis

The study used predicted docking scores and server-generated property outputs. No statistical hypothesis testing or experimental biological activity measurements were reported.

3. Results

3.1 Binding-pocket prediction

DoGSiteScorer identified pocket P0 as the selected pocket for SLC7A11, with a reported drug score of 0.85, volume of 815.94 Å³ and surface area of 981.45 Å². The pocket was selected for subsequent docking based on these predicted structural features.

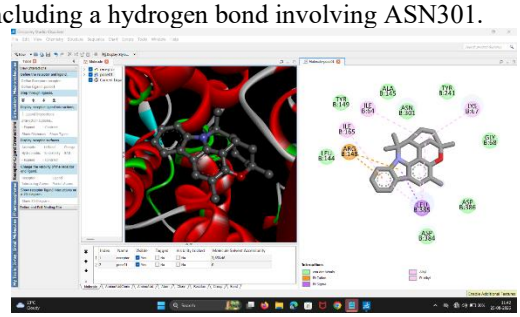
3.2 Docking scores of selected compounds

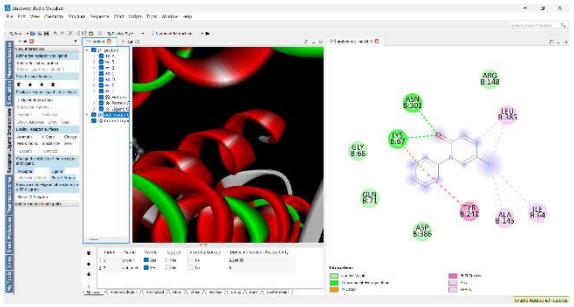
The thesis reports predicted docking scores for selected M. koenigii compounds against SLC7A11 and GPX4. Murrayazoline had the most favourable score against SLC7A11 among the compounds listed in the table (−9.1 kcal/mol). For GPX4, isomahanine had the most favourable listed score (−8.2 kcal/mol).

Compound	SLC7A11 score (kcal/mol)	GPX4 score (kcal/mol)
Pirfenidone	−6.3	−5.6
Murrayazoline	−9.1	−7.5
Mahanimbicine*	−8.3	−8.0
Muknicine*	−7.8	−7.0
Isomahanine	−8.8	−8.2
Girinimbine	−8.0	−7.7
Koenimbine	−8.4	−7.7
Mahanimbine	−8.5	−7.7
Mahanine	−8.3	−7.8
Murrayamine-C	−8.8	−7.3

3.3 Murrayazoline interaction profile with SLC7A11

The selected Murrayazoline–SLC7A11 pose was reported to occupy pocket P0 with a docking score of −9.1 kcal/mol. The interaction analysis listed TYR149, ILE64, LYS67, GLY68, LEU144, ARG148, ALA145, ILE165, ASN301, LEU385, ASP384 and ASP386 as nearby residues. The thesis describes hydrophobic/π contacts involving ILE64, ILE165 and LEU385, a π-cation interaction involving ARG148, and van der Waals contacts involving several other residues. The corresponding pirfenidone pose was reported to involve ASN301, LYS67, TYR241, LEU385, ALA145 and ILE64, including a hydrogen bond involving ASN301.





Reported property	Murrayazoline result
Molecular formula	$C_{23}H_{25}NO$
Molecular weight	331.19 g/mol (MolSoft table); 331.45 g/mol elsewhere in thesis
Consensus LogP	4.83
MolLogP	6.10
Predicted aqueous solubility	0.45 mg/L
MolSoft drug-likeness score	−0.62
SwissADME gastrointestinal absorption	High (predicted)
Blood–brain barrier penetration	Not predicted (SwissADME)
PAINS / Brenk alerts	0 / 0

3.4 Predicted toxicity

ProTox 3.0 classified Murrayazoline as toxicity class 4 and predicted an LD_{50} of 750 mg/kg. The thesis reported predicted active flags for neurotoxicity (probability 0.58), respiratory toxicity (0.74), immunotoxicity (0.87), blood–brain barrier toxicity (0.95) and ecotoxicity (0.70). Hepatotoxicity, cardiotoxicity, cytotoxicity, clinical toxicity and nutritional toxicity were reported as inactive by the model. These are model outputs, not observed toxic effects.

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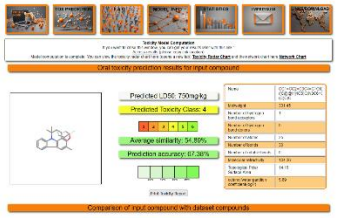
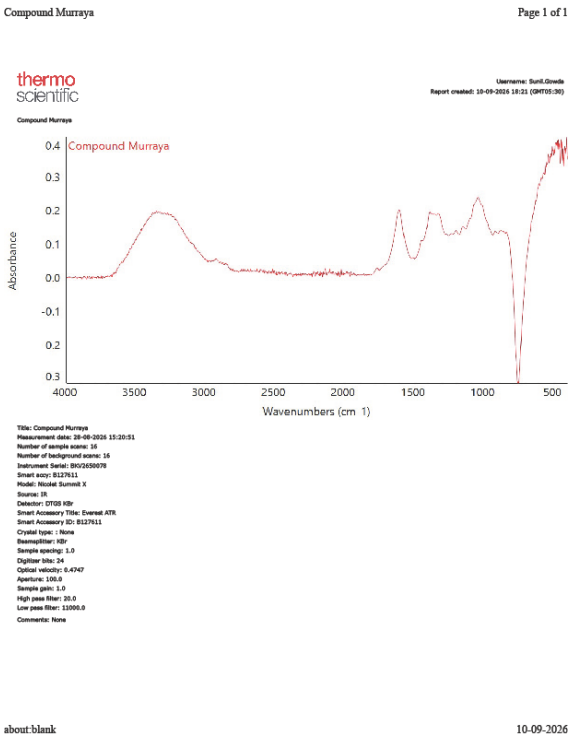


3.5 FTIR observations

The reported FTIR spectrum of the crude methanolic extract contained absorption regions at approximately 3270–3300, 2900, 1600, 1400–1300, 1250–1000 and 800–700 cm^{-1}. The assignments are tentative because crude extracts contain multiple compounds and overlapping bands. FTIR findings do not establish the identity or quantity of individual alkaloids.



IV. Discussion

This computational screening identified Murrayazoline as the compound with the most favourable reported docking score against SLC7A11 among the listed candidates. The score of −9.1 kcal/mol was more negative than the −6.3 kcal/mol reported for pirfenidone under the study's docking setup. The interaction diagram placed Murrayazoline near residues including ILE64, LYS67, ARG148, ILE165 and LEU385. These findings support a hypothesis that the compound can be accommodated within the selected predicted pocket, but they do not demonstrate direct binding or inhibition of SLC7A11.

The biological interpretation requires particular care. SLC7A11 regulates cystine uptake and contributes to glutathione-dependent antioxidant defence; the effect of modulating this pathway can vary by cell type and disease context. A more favourable docking score does not establish that Murrayazoline modulates ferroptosis in a beneficial direction, nor does it show an antifibrotic effect in lung tissue. In addition, pirfenidone is an established antifibrotic medicine but is not necessarily a validated SLC7A11-binding control. The rationale for comparing its docking score at this target should be explained, and a target-relevant positive control or docking validation strategy should be considered.

The predicted ADME profile presents both favourable and unfavourable features. High predicted gastrointestinal absorption and no predicted BBB penetration may be useful preliminary descriptors, while the high lipophilicity, low predicted solubility and negative MolSoft drug-likeness score raise concerns for compound handling and development. Toxicity predictions also flag potential endpoints requiring investigation. These predictions should be used to prioritize follow-up work, not to claim clinical safety or toxicity.

The plant-extract work provides contextual phytochemical information, but the thesis does not report isolation, quantitative identification or analytical confirmation of Murrayazoline in the prepared extract. The selected alkaloids appear to have been obtained from databases for docking. Consequently, the manuscript should not imply that the extract was shown experimentally to contain each docked compound. The FTIR analysis of a crude extract is insufficient to confirm a specific alkaloid.

Several methodological limitations affect reproducibility and interpretation. The thesis does not fully document docking settings or validation, and there are inconsistent compound names and molecular-weight values in the results. The stated objectives mention additional targets, including GPX4 and "GCSL4," while the main detailed results focus on SLC7A11 and provide a score table for GPX4. The identity and results for the additional target should be verified; "GCSL4" should not be silently corrected without checking the original records. A validated docking workflow,

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reproducible parameters, careful ligand identity checking and experimental confirmation would strengthen the study.

V. Limitations

This study is limited by its computational nature and the absence of biochemical, cellular or animal validation. The reported docking results do not confirm binding, target inhibition, ferroptosis modulation or antifibrotic activity. The docking protocol lacks some details required for independent reproduction, including full grid-box parameters and validation results. The crude-extract FTIR analysis cannot confirm the presence or concentration of Murrayazoline. Predicted ADME and toxicity outputs are subject to model uncertainty. Compound-name inconsistencies and discrepancies in reported molecular weight require resolution against original ligand and server outputs.

VI. Conclusion

In this study, Murrayazoline showed the most favourable reported docking score against SLC7A11 among the listed Murrayakoenigii-derived candidates (−9.1 kcal/mol), compared with −6.3 kcal/mol for pirfenidone. The predicted interaction profile and computational ADME/toxicity results nominate Murrayazoline for further investigation but do not establish target engagement, therapeutic efficacy or safety in pulmonary fibrosis. Future work should verify ligand identity and docking reproducibility, validate the docking protocol, confirm compound presence and purity where relevant, and test SLC7A11-related activity and antifibrotic effects in appropriate experimental systems.

Declarations

Ethics approval: Not applicable to the computational analyses and plant-extract procedures as reported; authors should confirm whether institutional approval or documentation was required for plant collection and any other procedures.

Funding: [Confirm funding source or state “No external funding was received.”]

Conflicts of interest: [All authors should confirm and approve the final statement.]

Author contributions: [Complete with all authors using their actual contributions; do not assign roles without confirmation.]

Data availability: [Provide docking input/output files, ligand identifiers, server reports and any other supporting data, or state where these can be accessed.]

Acknowledgements: [Add guide/supervisor acknowledgement only with approval and consistent with journal authorship criteria.]

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